Medullary Thyroid Cancer: A Case Series and Review of the Literature

Medüller Tiroid Kanseri: Bir Olgu Serisi ve Literatürün Gözden Geçirilmesi

Medullary Thyroid Cancer

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Özet

Amaç: Medüller tiroid kanseri, tüm tiroid kanserlerinin yaklaşık % 5'ini oluşturur. Burada, bu nadir malignitenin klinik ve tanısal özelliklerinin, cerrahi ve onkolojik sonuçlarının araştırılması amaçlanmıştır. Gereç ve Yöntem: 2010 ve 2015 yılları arasında medüller tiroid kanseri nedeniyle tiroidektomi ameliyatı yapılan 12 hasta retrospektif olarak değerlendirildi. Bulgular: Yaş ortalaması 57.2 yıl olan 12 (7 erkek ve 5 kadın) tiroid medüller kanseri hastası vardı. Boyunda kitle en sık (% 100) başvuru semptomu idi. Hiperkalsitoninemi 10 (% 83.3) hastada saptandı. Soliter nodül 7 (% 58.3) hastada saptandı ve en sık sonografi bulgu idi; şüpheli servikal lenfadenopati ise 3 (% 25) olguda tespit edildi. Total tiroidektomi minimum cerrahi yaklaşım idi. Santral ve lateral boyun diseksiyonları sırasıyla 10 ve 3 hastada uygulandı. RET mutasyonu 3 olguda saptandı. Izlem süresi boyunca üç (% 25) hastada nüks gelişti. Tüm nüksler bölgesel nükslerdi. Tartışma: Medüller tiroid kanserinin yönetimi diğer sık görülen tiroid kanserlerinden farklıdır. Genetik tarama ve ailesel sendromların araştırılması her zaman tanısal algoritmada standart bir araç olarak akılda tutulmalıdır. Total tiroidektomi ile birlikte santral boyun diseksiyonu minimal cerrahi yaklaşım olmalıdır. Tüm hastalar, yüksek rekürrens oranı nedeniyle cerrahi sonrası yakın takip edilmelidir.

Anahtar Kelimeler

Medüller Tiroid Kanseri; Tanı; Tedavi

Abstract

Aim: Medullary thyroid cancer accounts for approximately 5% of all thyroid cancers. Herein, we aim to investigate the clinical and diagnostic characteristics, surgical, and oncological outcomes of this uncommon malignancy. Material and Method: A total of 12 patients who underwent thyroidectomy for medullary thyroid cancer between 2010 and 2015 were retrospectively analyzed. Results: There were 12 MTC patients (7 males and 5 females) with a mean age of 57.2 years. Neck mass was the most common (100%) presenting symptom. Hypercalcitoninemia was found in 10 (83.3%) patients. Solitary nodule (7, 58.3%) was the most frequent sonographic finding, and suspicious servical lymphadenopathy was detected in 3 (25%) cases. Total thyroidectomy was the minimum surgical approach. Central and lateral neck dissections were performed in 10 and 3 patients, respectively. RET mutation was found in 3 cases. Three (25%) patients developed recurrence during the follow-up period. All recurrences were locoregional. Discussion: The management of medullary thyroid cancer is different than for other common thyroid cancers. Genetic screening and the investigation of familial syndromes should be always kept in mind as a standard tool in the diagnostic algorithm. Total thyroidectomy plus central neck dissection should be the minimal surgical approach. All patients should also be closely followed up after surgery, due to high recurrence rate.

Keywords

Diagnosis; Medullary Thyroid Cancer; Treatment

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Introduction

Thyroid cancer is the most frequent type among all endocrine malignancies, with its rapidly increasing incidence worldwide [1]. These cancers exist in four major subtypes based on histopathological features: papillary, follicular, medullary, and anaplastic. Medullary thyroid cancer (MTC) compromises approximately 5% of all thyroid cancers; differentiated forms including papillary and follicular cancers constitute the majority of cases [2]. Unlike the differentiated thyroid cancers, MTC originates from parafollicular C cells which secrete a variety of peptide hormones such as calcitonin, serotonin, and vasoactive intestinal peptide; therefore, it is accepted as a neuroendocrine tumor. Among these bioactive peptides, calcitonin is a specific biomarker with a high sensitivity in the diagnosis of MTC.

This uncommon thyroid cancer usually develops sporadically (75%) whereas close to one-fourth of cases are in hereditary forms including multiple endocrine neoplasia type 2 (MEN 2A and 2B) and isolated familial type [3]. These hereditary forms are caused by an activating mutation in the 'rearranged during transfection' (RET) gene, so genetic testing is of great importance in the initial management of MTC patients. The prognosis of MTC is worse than for differentiated thyroid cancers, with a 10-year survival rate of 95.6% in cases localized to the thyroid gland, but only 40% for the metastatic disease [4].

In this paper, we aim to review the clinicopathological features, diagnostic and therapeutic challenges, genetic characteristics, and prognosis of MTC through 12 cases who were treated and followed up in a tertiary medical center in Turkey.

Material and Method

Patients and study design

Among the 418 patients who underwent thyroidectomy for thyroid malignancy in a tertiary reference hospital in Ankara between 2010 and 2015, 16 (3.8%) cases were diagnosed as MTC at the final pathology. Four patients were excluded from the study due to irregular medical records; therefore data of 12 cases were analyzed.

Patients' characteristics such as age, gender, past history of thyroiditis, family history of thyroid disease, radiation exposure, comorbid systemic diseases, and the initial clinical symptoms and findings were recorded. Preoperative laboratory investigations including complete blood counts, routine biochemistry analysis, f-T3, f-T4, TSH, thyroglobuline, anti-TPO, calcitonin, and CEA, ultrasonographic and other radiological findings, and histopathological features obtained by FNAC were also noted in detail. All cases were screened for RET mutation and were evaluated in terms of hereditary MTC, with laboratory tests of serum calcium and 24-urinary metanephrines.

Treatment and follow-up

Total thyroidectomy plus central node dissection was the treatment of choice for all the patients as a standard surgical approach, and all perioperative complications were recorded. The patients were examined at regular intervals after surgery, with general examinations, calcitonin and CEA measurements, and appropriate radiological tests. A genetic screening was also performed for the relatives of cases diagnosed with hereditary MTC.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS 21.0 software, IL-Chicago- USA) was used for data analyses. Descriptive analysis was done for demographic and clinical features. The results were presented as mean±SD/percentages for continuous variables, and number/percentage for categorical variables.

Results

There were 12 MTC patients (7 males and 5 females) with a mean age of 57.2 years. There was no past history of thyroiditis, radiation exposure, or a family history of MTC. Neck mass was the most common (100%) presenting symptom while two (16.6%) patients also suffered from shortness of breath. Routine laboratory tests including complete blood counts and biochemical profiles were all within the normal limits. All the cases were euthyroidic at the time of diagnosis, and none had previously received any antithyroidal drug. Hypercalcitoninemia was found in 10 (83.3%) patients while CEA was elevated in only three cases (25%). The demographic data, clinical characteristics, and laboratory findings of all patients are presented in Table 1.

Table 1. Clinical data, sonographic findings, and pathological characteristics of the patients (n= 12)

Characteristics	n (%)
Age (y)	57.25±11.4 (39-78)
Gender	
male	7 (58.3%)
female	5 (41.7%)
Family history	Nil
Exposure to radiation	Nil
Thyroid function	Euthyroid (100%)
Elevated CEA	3 (25%)
Hypercalcitoninemia	10 (83.3%)
Clinical presentation	
Neck mass	12 (100%)
Shortness of breath	2 (16.7%)
Disphagia	1 (8.3%)
Pain at thyroid zone	1 (8.3%)
US findings	
Solitary nodule	7 (58.3%)
Multiple nodules	5 (41.7%)
Microcalcification	5 (41.7%)
Pathological servical lymph node	3 (25%)
Dominant nodule size (mm)	24.2±11.2 (15-52)
Diagnosis on FNAC	
Non-diagnostic	3 (25%)
Benign	4 (33.3%)
Medullary cancer	3 (25%)
Findings consistent with papillary cancer	2 (16.7%)

Age and dominant nodule size were presented as mean±SD (range); other variables were presented as number (percentage). y: year, mm: milimeter

US was the first step radiological method in the diagnostic work-up of the patients. Solitary nodule was detected in 7 (58.3%) cases; however, the remaining patients (5, 41.7%) had thyroid glands in multinodulary pattern. The mean size of dominant nodule was 24.2 mm, and suspicious lymphadenopathy in

the lateral neck compartment was detected in 3 (25%) cases. FNAC was performed in all patients, 3 of whomhad a suspicion of MTC (Table 1).

Total thyroidectomy was the minimal surgical approach. Central and lateral neck dissections were performed in 10 and 3 patients, respectively. All patients had a unilateral tumor with a mean size of 12.5 mm. Two patients had transient hypocalcemia while transient hoarseness occurred in one case.

All patients were screened for genetic mutation of RET, and VAL804 gene mutation of RET at the exon 14 was found in 3. Genetic screening was also performed for their family members. RET mutation was found positive in the children of a patient, and thus total thyroidectomy plus central dissection was performed for those.

Three (25%) patients who had servical lymphatic metastasis at the initial surgery developed recurrence during the follow-up period. All recurrences were locoregional, so lateral neck dissection was performed. All operative data, pathological findings, and oncological outcomes are presented in Table 2.

Table 2. Perioperative findings and oncological outcomes of the patients (n= 12)

Characteristics	n (%)
Type of surgery	
Totally thyroidectomy alone	2 (16.7%)
Totally thyroidectomy with central dissection	10 (83.3%)
Lateral neck dissection	3 (25%)
Tumor size (mm)	12.5±6.6 (3-26)
Presence of central lymph metastasis	4 (33.3%)
Presence of servical lymph metastasis	3 (25%)
Lymphatic invasion	4 (33.3%)
Vascular invasion	5 (41.7%)
Perineural invasion	7 (58.3%)
Extra thyroidal invasion	2 (16.7%)
Multifocality	1 (8.3%)
Bilaterality	Nil
Postoperative complication	
Temporary hypocalcemia	2 (16.7%)
Temporary hoarseness	1 (8.3%)
RET mutation	3 (25%)
Duration of follow-up (mo)	26.9±14.4 (8-48)
Recurrence	3 (25%)

Tumor size and duration of follow-up were presented as mean±SD (range); other variables were presented as number (percentage). mm: millimeter, mo: month

Discussion

Sporadic and familial hereditary forms of MTC have various clinical presentations as well as genetic features. The patients with sporadic MTC are usually in their fifth or sixth decade, with a slight female preponderance. However, the hereditary forms have a younger onset, of which MEN2A and familial thyroid cancer typically present when patients are in their 30s, and MEN2B usually presents in those younger than age 20. In our case series, 10 of 12 patients were diagnosed as sporadic MTC, with a median age of 55 years. On the other hand, our 2 cases with hereditary MTC did not have an earlier age of presentation compared with the sporadic ones, probably due to the small number of patients in our study.

Sporadic MTC usually presents as a painless solitary thyroid nodule; however, multifocality and bilaterality are more common in the hereditary forms [5]. Similarly, asymptomatic solitary nodule was the most common initial finding in our patients with sporadic MTC, and one of 2 hereditary cases had multifocal tumor. In addition, shortness of breath and disphagia were present in two and one patients, respectively; however, these findings were related to the large size of the thyroid gland, not to the extrathyoidal invasion of the tumor. At the time of diagnosis, neck lymph node metastases are detected in approximately 50% of cases, while distant metastases occur in 10% of cases [6]. The patients with large tumor size or multifocal tumors are reported to be at high risk of lymph node involvement [7]. However, in our study, servical lymph node metastasis was found in only 2 patients who had a tumor larger than 2 cm, and no distant metastasis was detected at the time of diagnosis.

In some MTC patients, hormonal symptoms such as flushing and diarrhea caused by excess secretion of calcitonin may be the initial clinical presentation [8]. Moreover, a small number of patients may present with systemic manifestations due to secretion of several peptides and substances, including vasoactive intestinal peptide, chromogranin A, bombesin, neurotensin, carcinoembryonic antigen (CEA), somatostatin, and adrenocorticotropic hormone (ACTH). Among these patients, excessive secretion of ACTH can result in the 'ectopic ACTH syndrome' [9]. Only 3 patients suffered from diarrhea at diagnosis although the majority of cases had hypercalcitoninemia. It is well known that serum calcitonin level has been routinly used as a specific tumor marker with high sensitivity rate for MTC diagnosis [10,11]. It is also useful in detecting recurrence after surgery. However, many physiologic and pathologic conditions such as physical activity, hypergastrinemia, hypercalcemia, renal insufficiency and proton pump inhibitory drugs are also related to hypercalcitoninemia, and only up to 40% of all cases with high levels of calcitonin associated with a thyroid nodule actually have MTC [12]. Therefore, calcitonin screening is not routinely recommended in the guidelines of the American Thyroid Association (ATA). It should be also noted that a normal preoperative calcitonin value cannot always exclude the diagnosis of MTC [13]. The other biomarker, carcinoembryonic antigen (CEA), is also produced by neoplastic C cells, and is widely used as a prognostic tool during the follow-up of the MTC patients, especially when preoperative serum calcitonin values are negative [14]. CEA is found in >50% of MTC patients, and the values of 30 ng/ml and above highly indicate the inability to cure the patient with surgical intervention and indicate a poor prognosis [15]. In addition, CEA level greater than 100 ng/mL was reported to be associated with extensive lymph node involvement and distant metastasis [13]. In our study, CEA was not a standard part of the preoperative diagnostic work-up, but it was routinely screened during the follow-up period, in addition to calcitonin. However, except in one case, CEA was not elevated in patients who developed recurrence.. High serum calcitonin levels were found in all patients with reccurrence. Chromogranin A is another useful diagnostic and prognostic marker in patients with MTC, but it can be elevated in many other neuroendocrine tumors [16]. This biomarker was not routinely used in the pres-

ent study.

In the diagnostic work-up of a patient presenting with a thyroid nodule, a family history of MTC, the presence of the symptoms and signs associated with pheochromocytoma, hyperparathyroidism, or MEN-2 syndromes should alert the physician to the potential diagnosis for MTC. Subsequently, neck US should be performed as in the classic approach to thyroid nodules. MTC has no pathogonomic feature on US; however it can be useful to show the nodule characteristics, additional thyroid pathologies, and the presence of enlarged lymph nodes, and to perform FNAC on the suspicious nodules. CT or MR of the chest and the neck can provide useful information when the lymphatic involvement extends into the mediastinum or deeper parts of the neck. In our study, US and FNAC were performed in all patients as the first step in the diagnostic algorithm. On US, 7 patients had solitary nodule while multinodularity was found in the remaining 5 cases. Additionally, sonographic enlarged and suspicious regional lymph nodes were detected in only 3 patients with MTC.

In most cases with MTC, FNAC cannot provide a definitive diagnosis before surgery. Similarly, the diagnosis of MTC was obtained by FNAC in only 3 patients preoperatively. The presence of stromal amyloid without thyroid follicles are the main cytological characteristics. Immunstaining for calcitonin, chromogranin A, or CEA can also help confirm the diagnosis. C-cell hyperplasia is another histopathological entity, which is usually considered a precursor of malignancy in hereditary disease. However, its implication in non-hereditary disease is controversial [13]. Similarly, 2 of the 4 cases with C-cell hyperplasia were diagnosed as hereditary MTC.

All cases were evaluated in terms of accompanying hereditary syndromes including isolated familial type, MEN 2A and 2B. Among the hereditary forms, MEN2A is the most common type (up to 90% of hereditary MTC) which contains MTC (100%), phaeochromocytoma (50%), and hyperparathyroidism (20%). Cutaneous lichen amyloidosis and Hirschsprung's disease are the other minor manifestations of MEN 2A. The second subtype, MEN 2B, comprises some 5–10% of MEN syndromes, and comprises MTC (100%), phaeochromocytoma (50%), marfanoid habitus, enteric ganglioneuromas, mucosal neuromas of the tongue, lips and subconjunctival areas and medullated corneal-nerve fibres. Isolated familial MTC is characterised by the absence of hyperparathyroidism or pheochromocytoma in two or more family generations or the presence of mutations in the RET oncogene. In our study, the majority of the patients were classified as sporadic MTC in accordance with the literature. Biochemical investigations such as urinary VMA, metanephrine, and radiological evaluation such as abdomen CT and MR were performed for all cases to detect the presence of clinical manifestations related to MEN syndromes. However, no disorders related to MEN syndromes were found in our patients, and therefore the two hereditary MTC patients with RET mutations were classified as familial MTC.

Genetic analysis was also one of the main parts of the diagnostic work-up of patients included the study. It is known that mutated RET gene is found in virtually all cases with MEN 2 syndrome while approximately half of the sporadic MTC patients carries this mutation [17,18]. In the present study, mutated RET gene was detected in 2 cases with hereditary disease; however, only 3 of 10 patients diagnosed as sporadic MTC had this mutated gene.

Total thyroidectomy with central lymph node dissection should be the treatment of choice for the MTC patients at a minimum. Most of the cases with a palpable tumor have metastasis in the central nodal compartment, and thus central lymph node dissection provides more curability than total thyroidectomy alone [19]. Ipsilateral neck dissection is required when enlarged/suspicious lymphadenopathies are detected by US or physical exam, central compartment lymph nodes are involved, or the primary tumor size is larger than 1 cm. In our study, the majority of cases underwent total thyroidectomy plus central dissection while lateral neck dissection was performed in 2 patients with metastasis in the servical lymph nodes. Total thyroidectomy alone was performed in two patients with benign FNAC. Additional central dissection was not performed due to the good prognostic features of the tumor and the unwillingness of patients to have another operation. The surgical management of the patients with MEN syndromes is different from the cases with isolated MTC because of the co-existing diseases including phaeochromocytoma and hyperparathyroidism. All patients with hereditary MTC should be screened for these diseases. If present, phaeochromocytoma must be removed surgically prior to thyroid surgery, due to the potentially lethal risks of anaesthesia. For the patients with a single adrenal tumor, unilateral adrenalectomy or a cortical-sparing surgery is an efficient approach. However, cortical-sparing surgery on at least one side, with close monitoring of the residual tissue, is offered for the cases with a single adrenal gland, or the patients with bilateral tumors [20]. In patients with MEN 2A, hyperparathyroidism is usually caused by one or more parathyroid adenomas. Therefore, if present, removal of the enlarged parathyroid glands should be performed at the time of thyroidectomy [21]. There was no MEN syndrome in our study, thus no such operations were needed.

MTC originates from parafollicular C-cells which do not accumulate iodine, and therefore radioactive iodine (RAI) therapy has no place in its management. In a study by Meijer et al [22], no significant additional value of RAI was found in the treatment of all MTC subtypes. In accordance, RAI was not a part of our therapeutic approach to MTC patients. Both radiation therapy and conventional chemotherapy have limited efficacy in patients with MTC. In recent years, several emerging treatment options targeting the RET receptor tyrosine kinase have been reported. Among those, vandetanib and cabozantinib are approved by the U.S. Food and Drug Administration, and are recommended for the the treatment of progressive and metastatic MTC [23,24]. Neither chemoradiotherapy nor other targeted therapies were applied in the study group.

In conclusion, MTC is a rare form of thyroid malignancy and its management should be different than for other common differentiated thyroid cancers. Genetic screening and the evaluation of familial syndromes should always be a standard part of the diagnostic work-up in MTC patients. Initial surgery has a very crucial role in the management of patients with MTC, and therefore, at a minimum, must be a total thyroidectomy plus central neck dissection. All patients should be closely followed

up after surgery, due to high recurrence rate.

Competing interests

The authors declare that they have no competing interests.

References

1. Pellegriti G, Frasca F, Regalbuto C, Squatrito S, Vigneri R. Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. J Cancer Epidemiol 2013;2013:965212.
2. Links TP, Verbeek HH, Hofstra RM, Plukker JT. Endocrine tumours: progressive metastatic medullary thyroid carcinoma: first- and second-line strategies. Eur J Endocrinol 2015;172(6):241-51.
3. Kouvaraki MA, Shapiro SE, Perrier ND, Cote GJ, Gagel RF, Hoff AO, et al. RET proto-oncogene: a review and update of genotype-phenotype correlations in hereditary medullary thyroid cancer and associated endocrine tumors. Thyroid 2005;15(6):531-44.
4. Sippel RS, Kunnimalaiyaan M, Chen H. Current management of medullary thyroid cancer. Oncologist 2008;13(5):539-47.
5. Cakir M, Grossman AB. Medullary thyroid cancer: molecular biology and novel molecular therapies. Neuroendocrinology 2009;90(4):323-48.
6. de Groot JW, Plukker JT, Wolffenbuttel BH, Wiggers T, Sluiter WJ, Links TP. Determinants of life expectancy in medullary thyroid cancer: age does not matter. Clin Endocrinol 2006;65(6):729-36.
7. Machens A, Hauptmann S, Dralle H. Increased risk of lymph node metastasis in multifocal hereditary and sporadic medullary thyroid cancer. World J Surg 2007; 31(10):1960-5.
8. Strosberg JR. Update on the management of unusual neuroendocrine tumors: pheochromocytoma and paraganglioma, medullary thyroid cancer and adrenocortical carcinoma. Semin Oncol 2013;40(1):120-33.
9. Hoff AO, Hoff PM. Medullary thyroid carcinoma. Hematol Oncol Clin North Am 2007;21(3):475-88.
10. Brandi ML, Gagel RF, Angeli A, Bilezikian JP, Beck-Peccoz P, Bordi C, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 2001;86(12):5658-71.
11. Maia AL, Siqueira DR, Kulcsar MA, Tincani AJ, Mazeto GM, Maciel LM. Diagnosis, treatment, and follow-up of medullary thyroid carcinoma: recommendations by the Thyroid Department of the Brazilian Society of Endocrinology and Metabolism. Arq Bras Endocrinol Metabol 2014;58(7):667-700.
12. Borget I, De Pouvourville G, Schlumberger M. Editorial: Calcitonin determination in patients with nodular thyroid disease. J Clin Endocrinol Metab 2007;92(2):425-7.
13. Roy M, Chen H, Sippel RS. Current understanding and management of medullary thyroid cancer. Oncologist 2013;18(10):1093-100.
14. Machens A, Schneyer U, Holzhausen HJ, Dralle H. Prospects of remission in medullary thyroid carcinoma according to basal calcitonin level. J Clin Endocrinol Metab 2005;90(4):2029-34.
15. Machens A, Dralle H. Pretarget anti-carcinoembryonic-antigen radioimmunotherapy for medullary thyroid carcinoma. J Clin Oncol 2006;24(20):e37.
16. Chen H, Sippel RS, O'Dorisio MS, Vinik AI, Lloyd RV, Pacak K, et al. The North American Neuroendocrine Tumor Society consensus guideline for the diagnosis and management of neuroendocrine tumors: pheochromocytoma, paraganglioma, and medullary thyroid cancer. Pancreas 2010;39(6):775-83.
17. Cerrato A, De Falco V, Santoro M. Molecular genetics of medullary thyroid carcinoma: the quest for novel therapeutic targets. J Mol Endocrinol 2009;43(4):143-55.
18. Agrawal N, Jiao Y, Sausen M, Leary R, Bettegowda C, Roberts NJ, et al. Exomic sequencing of medullary thyroid cancer reveals dominant and mutually exclusive oncogenic mutations in RET and RAS. J Clin Endocrinol Metab 2013;98(2):364-9.
19. Greenblatt DY, Elson D, Mack E, Chen H. Initial lymph node dissection increases cure rates in patients with medullary thyroid cancer. Asian J Surg 2007;30(2):108-12.
20. American Thyroid Association Guidelines Task Force, Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, et al. Medullary thyroid cancer: Management guidelines of the American Thyroid Association. Thyroid 2009;19(6):565-612.
21. Lundgren CI, Delbridg L, Learoyd D, Robinson B. Surgical approach to medullary thyroid cancer. Arq Bras Endocrinol Metabol 2007;51(5):818-24.
22. Meijer JA, Bakker LE, Valk GD, de Herder WW, de Wilt JH, Netea-Maier RT, et al. Radioactive iodine inthe treatment of medullary thyroid carcinoma: a controlled multicenter study. Eur J Endocrinol 2013;168(5):779-86.
23. Almeida MQ, Hoff AO. Recent advances in the molecular pathogenesis and targeted therapies of medullary thyroid carcinoma. Curr Opin Oncol 2012;24(3):229-34.
24. Hart CD, De Boer RH. Profile of cabozantinib and its potential in the treatment of advanced medullary thyroid cancer. Onco Targets Ther 2013;6:1-7.

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